



Office of Research and Development's (ORD) January 2007
Response to the Board of Scientific Counselors (BOSC) December
2006 Final Letter Report that Reviews ORD's National Center for
Computational Toxicology

BOSC Computational Toxicology Subcommittee:

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**ORD Response to Board of Scientific Counselors (BOSC) June 2006 Review of the
National Center for Computational Toxicology (NCCT)**

The following is a narrative response to the comments and recommendations of the BOSC review of ORD's National Center for Computational Toxicology that was held on June 19-20, 2006, in Research Triangle Park, NC. The review was conducted by a standing subcommittee of the BOSC. The subcommittee had previously reviewed the NCCT on April 25-26, 2005, and ORD had responded to that review on September 8, 2005. In the second review, the BOSC noted that in its 16 months of existence, "NCCT had made substantial progress in (1) establishing goals and priorities; (2) making connections within and outside EPA to leverage the staff's considerable modeling experience; (3) expanding its capabilities in informatics; and (4) significant contributions to research and decision-making throughout the Agency." Furthermore, they noted, "many of the recommendations made by the BOSC during its first review have been acted on by NCCT."

Following are specific comments related to the charge questions made by the committee. The charge questions are summarized in bold text, followed by the BOSC's comments in italics, and ORD's response to the comments in regular type. Attached to this document is a summary table of the BOSC comments and proposed ORD actions.

- 1. The first charge question asked for an evaluation of progress the Center made during the past year in developing and maximizing connections and collaboration within ORD and the rest of the Agency. Specifically, the committee was asked about interactions, including the established Communities of Practice (CoPs) and other notable examples and if there are other opportunities that NCCT should explore.**

All active CoPs have formal memberships and are chaired by NCCT staff. The Center also has observed active participation among numerous EPA laboratories and centers and several program offices. The Chemoinformatics and Chemical Prioritization CoPs already have demonstrated outreach to outside agencies, such as the National Institutes of Health (NIH), National Institute of Environmental Health Sciences (NIEHS), and National Toxicology Program (NTP). Some are working with or soliciting international and private sector collaboration. The CoPs have been effective in focusing on defining problems and suggesting solutions, agreeing on modeling approaches and database issues, and setting up forums and workshops for discussions. They will be responsible for leading a better coordinated effort within EPA and among agencies. The Subcommittee believes that establishing a Cumulative Risk CoP is worthy of pursuit. Such a CoP would provide significant opportunities to define areas for improvement in risk assessment practices and could provide inventory tools and other benefits. NCCT should consider whether it would like to provide a facilitator role or leadership role in this area.

Response: ORD appreciates the Committee's recognition of NCCT's current efforts. Also, ORD agrees on the importance of pursuing the formation of other relevant CoPs.

Due to the small size of the NCCT staff, ORD is concerned these could over tax the staff. NCCT is committed to supporting the three existing CoPs (Chemoinformatics, Chemical Prioritization, and Biological Modeling) and will take steps to ensure their vitality. For other CoP ideas, ORD will look across all the Labs and Centers to see if relevant similar work groups and committees are already established and could be amended to address such issues, or encourage the establishment of ones for which no precedent can be formed. In particular, we have further considered a CoP centered on Cumulative Risk, as proposed during the review. While still favoring the idea, we have realized from the activities of the existent CoPs that they function best when aligned along a well defined issue and have a commonly identified goal. For Cumulative Risk, our current opinion is the issue and goal of a dedicated CoP must be better refined, and we hope to work with other Agency scientists to foster this refinement and development.

With regard to other opportunities for exploration, the subcommittee suggested NCCT seek broader program office input. Additionally, CoPs covering areas such as Mixtures, Cross-Species Extrapolation, Population/Systems Dynamic Models, and Multimedia Fate and Effects Modeling should be considered for either NCCT use or ORD's broader use.

Response: ORD also agrees with the Committee's recommendation of broader program office input. The Center is in the process of increasing the number and frequency of contacts and meetings with Program and Regional Offices. Formal presentations are often part of those contacts. For example, we have recently given overview presentations of the program to EPA's Science Policy Council and Regional Risk Assessors, both of which drew considerable interest. In addition, we are scheduled to present a detailed overview of the ToxCast program to Office of Prevention, Pesticides, and Toxic Substances (OPPTS) on February 1, 2007, in Washington, D.C. Finally, the upcoming International Forum on Computational Toxicology being organized by NCCT on behalf of ORD is expected to provide opportunities for contact within and outside the Agency. NCCT is preparing and executing several means to better communicate progress, outputs, and abilities to the rest of the Agency, and in particular we are working on ways to improve the content of our internet site. NCCT staff are also organizing a series of short courses in the field of computational biology for Agency staff and others as well.

2. The second charge question dealt with interactions with the two newly funded STAR Environmental Bioinformatics Seminars.

Individually, the Bioinformatics Centers were viewed as excellent choices, each providing expertise and resources largely complementary to each other and to the NCCT with little overlap. Although both Centers are just beginning their work with EPA, there is great opportunity for synergy in developing new approaches for the analysis of toxicogenomic data and integration of diverse information necessary to place these data into an appropriate context. Integration of the external Bioinformatics Centers and the programs within NCCT will occur following hiring of

one senior and one junior bioinformatics scientist. This may not represent sufficient personnel, however, to allow NCCT to fully support its overall mission.

Response: NCCT is continuing to work with ORD's National Center for Environmental Research (NCER) to ensure the Bioinformatic Centers enhance the current state of the science in this critical research area. The hiring of Dr. Richard Judson as a Title 42 Senior Bioinformatician in NCCT has greatly facilitated the interactions with the Centers. Dr. Judson coordinates a monthly EPA-wide seminar program (Info on Informatics), which features one of the project areas from each of the Centers. The goal of the series is to promote EPA awareness of the objectives of the Centers and to help facilitate development of interactions with them. Drs. Judson and Kavlock, together with staff from NCER, performed a site visit to the University of Medicine & Dentistry of New Jersey (UMDNJ) Center in December, which resulted in very rewarding discussions concerning future interactions. A second site visit is planned for early 2007 by Dr. Judson and several other EPA scientists to further develop ties. Due to the geographical closeness, interactions with the University of North Carolina (UNC) Center have been more frequent and targeted. A predoctoral student has been identified to interact on matters related to genomic data storage, analysis and interpretation, and several interactions have developed in conjunction with the chemical prioritization efforts of the ToxCast program.

Consequently, NCCT needs to develop a more comprehensive strategic plan for data collection, management, and integration through creation of databases that model the structure of the underlying information and its potential use.

Response: Dr. Judson, working in conjunction with Dr. Imran Shah, our Title 42 Computational Systems Biologist (both joined the Center in September), has also taken the lead in developing an overall framework for information management within NCCT. In response to the strong recommendation of the BOSC related to the need to adequately address this topic, we propose a targeted briefing on our approach to information management and information technology for the BOSC sometime in the May-June 2007 time frame.

It was noted that there exists a need within the field for trained personnel in computational toxicology. In addition to the existing postdoctoral program, one feasible approach would be to institute a career development award similar to the NIH "K" awards that would provide mentored training and research to more senior personnel.

Response: We appreciate the recommendation to strengthen our training component, as we view this as one of our three critical functions (in addition to providing a service function to other ORD researchers and conducting innovative research on the use of computational models in risk assessment). We will work with appropriate human resource components within EPA to explore options for career development training of other scientists. We have also engaged advanced discussions within

NCCT on hosting several advanced training courses for EPA staff. Lead topics are Physiologically Based Pharmacokinetic Models and Chemical Prioritizations Tools.

3. The third charge question was designed to promote discussion about the potential of NCCT research programs making impacts on Agency function, and how well the NCCT was leveraging its resources in this regard.

The portfolio provided a mix of short- and long-term deliverables. Many of the former stand a good chance for application within program offices or other parts of ORD within months. The research programs included those from external institutions. NCCT has leveraged its limited resources to good effect.

Response: The NCCT program was designed with the goal of having some short-to intermediate- term deliverables, as well as some projects with longer timelines, and we appreciate the recognition of the value of this by the BOSC. We have continued to work to best leverage our resources, and present three examples of related efforts since the review. The first is the establishment of an Interagency Agreement with the National Chemical Genomics Center (NCGC) of the NIH to conduct quantitative, high throughput screening analysis of ToxCast chemicals against a number of nuclear receptor assays. This IAG provides NCCT with a direct link to NIH's Molecular Library Initiative. This Initiative will be providing extremely cost effective data to us over the next 5 years, as it taps into a well established infrastructure geared to running these types of assays. NCCT has also started a series of high level meetings with the management of the National Health and Environmental Effects Research Laboratory (NHEERL), the National Environmental Research Laboratory (NERL), and the National Risk Management Research Laboratory (NRMRL) to best define working relationships between these groups and how to target the computational toxicology resources available in those laboratories. The first of these meeting was held with NHEERL on January 18, 2007. Finally, we have been working closely with staff in NCER to define the next Request for Applications (RFA) in computational toxicology. The objective of this RFA will be to establish several academic centers working in areas of computational systems biology, and we are excited about the prospect of this activity to move us forward more rapidly in programs such as the Virtual Liver, as well as in developing the computer infrastructure and computational approaches to systems biology from a toxicological viewpoint.

One of the major aims of NCCT is to develop useful relational databases. This also presents a significant challenge in managing the information. The Center should develop a strategic plan for data integration and for constructing databases that should be considered as information models.

Response: As noted in the response to Q2, NCCT is developing a strategic plan for data information and management, and is prepared to bring its plan to the BOSC for comment within the next 6 months.

- 4. The fourth charge question consisting of three parts focused on NCCT's mission to accelerate the use of computational tools in the Agency mission. The first part more specifically asked the committee to comment on whether the proposed computational models have the potential to identify and reduce uncertainties associated with risk assessment.**

Yes, proposed computational models have the potential to identify and reduce uncertainties associated with risk assessment. Additional opportunities outside the mechanistic models (especially in biomarkers that indicate exposure but that are not immediately or directly linked to toxicological response) may exist to fulfill NCCT's mission.

Response: ORD is pleased the committee endorses the selection of computational models and the planned approach to develop, test, and use these models. ORD agrees there are other opportunities that can use other than mechanistic models including exposure biomarkers. Since the review, new expert staff have come on board with systems modeling expertise. Plans are being formulated for an extensive liver model that can simulate its molecular processes and predict the possible toxic effects of chemicals on liver function. As part of this effort, modules at many different levels and complexities will be formulated, including those that relate data to tissue outcome without detailed specific knowledge of mechanism. Further, work has now begun on computational approaches to apply advanced statistical and machine learning methods to evaluate human exposure and environmental health data. Target data include multiple types of biomarker and environmental exposure information.

The second part of the charge question addresses the models' ability to help identify susceptible populations and compare the risks to those populations with the risks to the general population.

Ultimately, these and other models within NCCT and outside the Agency can help identify susceptible populations. Appropriately, models currently are being developed for use in computational toxicology. Within 3-5 years, some of these models likely will be sufficiently developed and validated to address susceptibility. "Susceptible populations" may be defined to include life stages, gender, race, socioeconomic group, species, and geographic distribution.

Response: ORD accepts this endorsement and will continue in its computational modeling activities to consider this an important goal.

The last part of this question asked whether there was sufficient coordination between model development and associated data to avoid having the models being either over- or under-determined.

Overall, data collection appears appropriately coordinated with model development. It will be important to validate models based on genomic methodologies given the inherent constraints in sample sizes, and other challenges, with these approaches.

Response: ORD agrees and recognizes the importance and challenge of validating and testing of all models. NCCT modelers have established close working collaborations with laboratory biologists and chemists who are conducting many of the experiments or gathering and using existing data for model building and testing.

5. The fifth charge question addressed whether the Computational Toxicology Implementation Plan described an achievable roadmap and set forth realistic milestones and outputs.

Each of the research areas is active. NCCT has a core strength in modeling, and is expanding its expertise in informatics. The Center is leveraging its position by outreach to other EPA labs and programs via internal research funding and communities of practice, and externally via STAR grants and the external bioinformatics centers. The addition of the informatics centers in particular strengthens NCCT's research in information technologies. This will be strengthened further through the hiring of NCCT staff with informatics expertise. The STAR grants greatly expand NCCT's capacities in the generation of high-information-content data sets that will be needed to support model development.

There are still some challenges that will need to be overcome in the areas of database development and management. More details are provided in our response to question 2. This will be especially important in the development and demonstration of biological models derived from complex data sets.

The research has milestones with nearer term and longer term time horizons, which is appropriate. It is clear that chemoinformatics tools and prioritization tools are well underway and are likely to be applied by risk assessors and regulators within the next few years.

Response: Some challenges remain that will need to be overcome in the areas of database development and management. More details are provided in our response to Question 2. This will be especially important in the development and demonstration of biological models derived from complex data sets. The Center will do whatever it can, within the boundaries of the grant process, to foster coordination of efforts between the two external bioinformatics centers and NCCT's internal program.

The BOSC recommends the NCCT develop a more detailed work plan for the virtual liver model, and that this plan be more extensively reviewed by the Computational Toxicology Subcommittee during its next annual review

Response: Development of the virtual liver model has gained momentum with the hiring of Dr. Imran Shah, a Title 42 Computational Systems Biologist. He has been leading biweekly discussions with relevant staff members from NCCT, NHEERL, NERL and NCEA to articulate reasonable goals and expectations for this effort. NCCT proposes we schedule a teleconference with the BOSC in the third quarter of

2007 to present a briefing and lead a discussion on development of the Virtual Liver activity.

6. The sixth charge question addressed the depth and breadth of the resources directed at fulfilling the Implementation Plan.

The subcommittee believes that the research program covers the range of thematic areas. Some areas, however, have deeper coverage than others. The areas of cumulative risk assessment and cross-species extrapolation are still under-represented, but given the state-of-the-science, it is appropriate to place limited emphasis on these areas for the next 3-5 years. The staffing additions in HTS, toxicogenomics, and biological modeling are all strong and have improved the strength and breadth of NCCT. The planned staff additions in bioinformatics will be critical to the continuing success of the Center. One of these additions should have strong skills in data management systems.

Response: We agree and the recently hired Title 42 scientists who are filling two critical gaps in our expertise. Their contribution will be evident when we brief the BOSC on our information management and virtual liver programs. Together, they provide expertise in informatics and advanced computational methods, and are working in key areas for the NCCT. We have reserved a more junior level position to support the programming needs of these two members, and are in the processing of re-orienting the support provided to us by the Environmental Modeling and Visualization Laboratory of the Office of Environmental Information, which has been supplying a variety of support activities to the Computational Toxicology Program for the past two years. Finally, we are in advanced discussions with a senior level scientist in the area of toxicogenomics. We will know shortly whether this additional Title 42 position within the NCCT will provide senior leadership in genomics.

7. The seventh charge question asked about evidence that NCCT is being responsive to program and regional office needs.

Most of the presentations addressed program office input in planning priorities and approaches.

Some projects formed to support program office issues, such as carbamate cumulative risk, DSSTox, and RefTox DB. The Subcommittee noted program office and regional office staff as co-principal investigators on various projects. The Implementation Plan references a role for the Computational Toxicology Implementation and Steering Committee (CTISC), which could be useful, if sustained.

Response: ORD thanks the committee for its response and encouragement. While ORD recognizes the usefulness of the CTISC, its role is being reevaluated to determine if, in its current state, this is the most effective manner to insure wide involvement and support from the Program and Regional Offices as well as others. As mentioned in our discussion under Question 1, we are engaging many other

opportunities, including the Communities of Practice, to this end. We are also taking the opportunity to brief various EPA groups about the research program, with recent presentations to the Science Policy Council, the Regional Risk Assessors (which consists of both EPA and state risk assessors involved in Superfund sites), and an upcoming presentation to the Office of Pesticide Programs.

8. The eighth charge question dealt with communication issues.

NCCT has components of both a research and service center—it both initiates and receives new ideas. For a young organization, NCCT has done very well in establishing communication with its collaborators, contractors, and some stakeholders. The establishment of CoPs and participation of internal clients is a good start to communication within the Agency. Also of note is NCCT's establishment of monthly videoconference presentations. Most of the other communication activities seemed to be investigator-initiated. Given that the Center plans to develop tools and methods that will be used by ORD and other EPA staff, NCCT should establish a regularly scheduled plan for communication and updates. This process will convey the sense that new ideas are welcomed by NCCT and allow NCCT to accept ideas and be aware of the needs of the program offices, regional offices, and stakeholders. The establishment of such a process will enhance the marketing of tools and methods developed by NCCT. One way to give Agency clients part ownership in the Center is to invite them to BOSC reviews, such as this, and ask them to share how they are using NCCT's methods, tools, and information. The Subcommittee recommends that NCCT communicate with the Regional Risk Assessor's Office and seek its representation. Within the past year, NCCT has commendably given 21 presentations to various offices within EPA to raise awareness.

Response: We agree and NCCT is paying close attention to this. Staff are regularly looking for and finding opportunities to interact with other scientists, organizations, and Agency programs. In addition to scientific publications and presentations, feature articles are often written, such as one in the January, 2007 issue of *EM* highlighting the research activities of NCCT. NCCT is in the process of enhancing the Computational Toxicology website to communicate more effectively and in a more timely fashion. A senior ORD communications staff member and an intern in the communications office are working with NCCT to develop, publish, and disseminate appropriate messages. We expect to be releasing periodic updates on progress in implementing the ToxCast program, and we just completed a fact sheet describing the Interagency Agreement we just signed with NCGC/NIH. This is the first tangible component of the ToxCast program. As the various supporting contracts are awarded over the next six months, we will be posting updates on our website. We also will be using the upcoming International Science Forum on Computational Toxicology to engage a large number of Agency scientists. Finally, as noted above, at their request we briefed the Regional Risk Assessors on the program, and received a number of emails following the presentation asking for additional details.

9. The ninth and final charge question asked if the current research program was designed to achieve environmental outcomes and how those outcomes could be measured.

The current program is designed to achieve environmental outcomes that are appropriate to the Agency. Potential measures to determine these outcomes include:

- ◇ *Use of screening models for chemical prioritization.*
- ◇ *Validation and use of genomics-associated biomarkers in field studies.*
- ◇ *Use of computational models in the risk assessment process in the long term.*
- ◇ *Success of databases (DSSTox, pesticides) in cleaning up and organizing disparate databases and making them widely useful to environmental science and regulatory communities.*
- ◇ *Use of specific models (such as virtual liver, pyrethroid metabolism, macromolecular modeling, physiologically based pharmacokinetic (PBPK) models, steroidogenesis models, cumulative risk models, and so forth, by broader environmental science and risk assessment communities.*

Response: ORD thanks the committee for these suggestions. NCCT is looking to develop specific ways to regularly gather information to apply to those measures. Progress and results will be shared with the committee at future meetings. Our current thinking is it would be best to engage the BOSC over the next year on specific projects, particularly ToxCast, the Virtual Liver, and our Information Management plans. As these are programs still in rapid phases of evolution, dialogue with the BOSC would be beneficial to use in refining their approaches. At the discretion of the BOSC, these could be done either in individual teleconferences over the next 6-9 months, or at a face-to-face meeting, focusing on the three topic areas.

We suggest the next all encompassing review of the program be held in the first half of 2008. At that time, we would have made considerable progress on a number of research fronts that would allow us to change the main purpose of the review from reviewing strategic directions to analyzing the research outcomes.